REMARKS

Claims 23-77 are pending in this application. Applicants have amended claims 47 and 77 solely in order to change their dependencies from claims 45 and 75 to claims 46 and 76, which recite "animal insulin." This Amendment does not introduce new matter or narrow the scope of the affected claims. Applicants respectfully request the entry of this Amendment.

Rejection of Claim 47 under 35 U.S.C. § 112, Second Paragraph

The Office rejected claim 47 for allegedly lacking sufficient antecedent basis. (Office Action at page 2.) Because Applicants have amended this claim, as well as claim 77, to depend directly from claims 46 and 76, which both recite "animal insulin," this rejection is now moot.

Rejection of Claims 23-46 and 48-77 for Obviousness-Type Double Patenting

The Office rejected claims 23-46 and 48-77 under the judicially created doctrine of obviousness-type double patenting over claims 1-11 and 16-22 of United States Patent No. 6,339,061. (Office Action at pages 2-4.) Applicants request the withdrawal of this rejection in light of the Terminal Disclaimer submitted with this response.

Rejection of Claims 23-34, 40-46, 48-64, and 70-77 under 35 U.S.C. § 103(a)

The Office alleged that claims 23-34, 40-46, 48-64, and 70-77 are obvious over the combination of Flaa et al. (WO96/27661; "Flaa"), Mikura et al. (EP 158487; "Mikura"), Ahmad et al. (*Journal of the American Oil Chemists' Society*, 60(4): 837-40 (1983); "Ahmad"), and Santha et al. (*Indian Journal of Animal Science*, 49(1): 37-41

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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(1979); "Santha").[1] (Office Action at pages 4-6.) The Office asserted that the combination of Flaa, Mikura, Ahmed, and Santha would have made it "obvious to a person of ordinary skill in the art to use cysteine as a reducing agent for protein storage." (Office Action at page 5.)

Applicants respectfully traverse this rejection. This combination of four references does not suggest to one of ordinary skill in the art to follow the claimed process of "adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of a protein during storage" such that "the effective concentration does not decrease by more than about 7%," or such that the delay occurs "during a period of greater than 24 hours." (Claims 23 and 48.)

As the Office acknowledged, Flaa does not teach using cysteine, but instead mentions several other reducing agents. (Flaa at page 11, lines 1-8.) Nor does it teach using "an amount of cysteine effective to delay the decrease in the effective concentration of the protein" for "a period of greater than 24 hours" or such that "the effective concentration does not decrease by more than about 7%." For example, in Figures 1-6, human troponin I generally retains only about 75-90% stability, based on an antibody binding test, after only 1-2 days of storage in the matrix composition of Flaa. The matrix of Flaa comprises only a small amount of reducing agent, about 0-5 mM, in a mixture of several other ingredients. In particular, Flaa uses a "stabilizing protein" like albumin, to stabilize insoluble proteins like troponin, myoglobin, CK, LD, and myosin. (Flaa at page 1, lines 4-11; page 7, lines 18-24; and page 9, line 23, to

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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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[1] The Office asserts that copies of these publications were submitted to Applicants with PTO form 892 in Paper No. 3. However, Applicants did not receive Paper No. 3. The undersigned thanks Examiner Chernyshev for confirming the citations.

page 11, line 8.) This implies that the protein additive rather than the reducing agent is of primary importance in providing stability.

Mikura discusses preparations of interleukin-2 (IL-2) which, as the Office acknowledged, do not contain cysteine. Instead, Mikura provides a long list of different kinds of reducing agents at page 3, lines 2-12. It also lists many types of amino acids, saccharides, and other possible additives. (Mikura at page 3, lines 13-19.) Examples 1-12 and Tables 1-12 all show the use of glutathione, ascorbic acid, or sodium ascorbate, rather than cysteine, in the IL-2 solutions.

The teachings of Flaa and Mikura taken together do not suggest to one of ordinary skill in the art to replace the reducing agents that they use with cysteine. These two publications as a whole simply provide a long list of possible reducing agents that conspicuously omits cysteine. While the Office contended that "cysteine is a well-known reducing agent" and "can be interchangeably used," the Office provided no information to substantiate this conclusory statement. (Office Action at page 5.) The Federal Circuit has recently pointed out that the Office "cannot rely on conclusory statements" in establishing a *prima facie* case of obviousness, "but must set forth the rationale on which it relies," and that "[t]his precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Lee*, 277 F.3d at 1343, 1345, 61 U.S.P.Q.2d at 1433, 1435 (Fed. Cir. 2002) (citations omitted).

Ahmad and Santha do not alleviate the deficiencies of the combination of Flaa and Mikura. They both discuss adding cysteine to fatty acids such as ghee, safflower, or sunflower oil, and not to any aqueous protein solution. Neither Ahmad nor Santha are in the field of Applicants' endeavor or reasonably pertinent to the problem with

FINNEGAN
HENDERSON
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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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which the present invention is concerned. (See M.P.E.P. § 2141.01(a) and citations therein.) No reason, suggestion, or motivation exists in any of the art cited for the skilled person to take cysteine from the food-based compositions of Ahmad and Santha and place it in the aqueous protein solutions of Flaa and Mikura and expect it to delay the temporal decrease of the effective concentration of the protein as claimed. Indeed, lipid and aqueous solutions have quite different chemical properties that would be expected to affect the behavior of reducing agents.

Further, as to the dependent claims, Applicants point out, for example, that none of these four publications mentions any insulin, insulin derivative, or insulin precursor. (See claims 46, 47, 76, and 77.) Nor do they discuss a "process comprising the renaturation of the heterologous protein . . . " as described in claims 45 and 75. Nor do they discuss situations "wherein the temporal decrease in the effective concentration of the protein is delayed for a period of 8 weeks or more." (See claims 53 and 54.) In summary, the combination of these publications does not rise to the level of a *prima facie* case of obviousness.

For all of the above reasons, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: October 8, 2002

By: Carol P. Einaudi

Carol P. Einaudi
Reg. No. 32,220

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX TO AMENDMENT OF October 7, 2002

Version with Markings to Show Changes Made

Amendments to the Claims

47. (Amended) The process as claimed in claim [45] 46, wherein the animal insulin is human insulin.

77. (Amended) The process as claimed in claim [75] 76, wherein the animal insulin is human insulin.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com